Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-020-05839-1

MATERNAL-FETAL MEDICINE

Does greater morning sickness predict carrying a girl? Analysis of nausea and vomiting during pregnancy from retrospective report

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Received: 1 May 2020 / Accepted: 13 October 2020
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Abstract

Purpose The prevalence of severe nausea and vomiting during pregnancy (NVP) requiring hospitalization has been associated with female fetal sex. However, the question of whether fetal sex and less severe forms of NVP share that association has not been investigated. The objective of this study was to evaluate the relationship between fetal sex and the frequency of NVP.

Methods We collected self-reported data from mothers via an international web-based survey on the Amazon Mechanical Turk (MTurk) platform about pregnancy and first trimester NVP history. We considered the covariables of maternal age, parity status, proneness to nausea, geographic cohort, and preconceived notions of a relationship between fetal sex and NVP.

Results Two-thousand five hundred and forty-three mothers met the inclusion criteria, yielding data from 4320 pregnancies. Women gestating a female fetus reported higher frequencies of NVP ($M = 6.35$ on a 1–9 scale) than did women gestating males ($M = 6.04$, $p = .007$). This effect held true when all other variables were included in the regression. General proneness to nausea, maternal age, and parity were also significant independent predictors of NVP.

Conclusions Women that carried a female fetus, as opposed to a male fetus, reported significantly higher frequency of NVP during the first trimester of pregnancy. Further research should evaluate both the proximate and ultimate causes of this relationship.

Keywords Nausea · Vomiting · Pregnancy · Fetal sex

Introduction

Worldwide, folk wisdom states that the presence and intensity of nausea and vomiting in pregnancy (NVP) is often predictive of fetal sex [1, 2]. According to this belief, if a pregnant woman does not experience frequent NVP, she will likely give birth to a boy. On the other hand, if a pregnant woman suffers particularly intense pregnancy nausea, the legend suggests that she will give birth to a girl.

Several studies have described an association between fetal sex and the presence of severe NVP (hyperemesis gravidarum). Whereas 70–80% of women report some degree of NVP [3], hyperemesis gravidarum, defined as severe NVP which if left untreated may lead to significant maternal and fetal morbidity [4], is a much rarer entity, occurring in 0.3–2% of women [5]. In a retrospective study of nearly 10,000 pregnant women in the United Kingdom, women presenting with hyperemesis gravidarum were significantly more likely to have a female fetus compared to those without hyperemesis gravidarum [6]. Similarly, a study performed in Israel found that pregnant women admitted to hospitals with the diagnosis of hyperemesis gravidarum were significantly more likely to be carrying a female fetus. This same study also found that women with hyperemesis gravidarum carrying male fetuses experienced a higher rate of adverse effects of hyperemesis gravidarum on pregnancy outcome, including an increased risk for preterm delivery and composite neonatal morbidity [7]. Another study also revealed that the odds of having a female infant was 50% greater in pregnant women

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00404-020-05839-1) contains supplementary material, which is available to authorized users.

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Published online: 24 October 2020

hospitalized with hyperemesis gravidarum during the first trimester than in cases of un-hospitalized pregnant controls [8]. This finding was corroborated by a similar trend in two studies of Swedish women, which found hyperemesis gravidarum to be over-represented in pregnancies when the infant was a girl [9, 10]. Female fetal sex apparently increases risk for severe NVP, but the presence of nausea and vomiting does not negatively impact the pregnancy outcome for the female fetus.

Although the interaction between NVP and fetal sex has been studied in cases of admission to the hospital due to hyperemesis gravidarum, the existence of such an association has not been explored at the lower severity of NVP experienced by the majority of pregnant women. The purpose of this study was to evaluate the relationship between fetal sex and the frequency of NVP at all levels of severity. We hypothesized that more frequent NVP is associated with female fetal sex, even for women not hospitalized with hyperemesis gravidarum.

Methods

Participants

We recruited women from Amazon's Mechanical Turk (MTurk), an online crowdsourcing marketplace that has become a common subject pool for social science research, and which has been found to yield comparable results to in-person lab studies [11]. MTurk's worker pool is international, but the vast majority of English workers are from the US and India [12]. As such, we attempted to recruit three cohorts of participants ('US', 'India', and other parts of the 'World') to enable a simple test of the cross-cultural reliability of any effects we found. Our inclusion criteria included woman over the age of 18 who had given birth to at least one biological child and spoke fluent English. The study was advertised on MTurk with the title: "Are you a mother? Take a 3 min survey on pregnancy." Participants were compensated $0.50 for participation. Participants provided informed consent before completing the survey.

Procedure

Participants completed a web-based survey about their experience with nausea and vomiting during pregnancy with each of their children (see Materials). Three data quality checks were dispersed throughout the questionnaire. Participants were debriefed about the purpose of the study at the end of the survey.

Materials

NVP questionnaire

Participants were initially asked how many biological children they had. They were then prompted to answer a series of questions about their pregnancy with each child. Information was gathered about the sex of the child and the mother's age during the pregnancy. Mothers were asked how often they experienced nausea and vomiting during the first trimester of each pregnancy (with the options of "more than once a day", "daily", "once every 1–2 days", "once every 3–4 days", "once a week", "once every 2–3 weeks", "once a month", "almost never", "never", and "I'm not sure"). Mothers were also asked to think about a time when they were NOT pregnant and answer how the statement "I am prone to nausea and/or motion sickness" best described them (with the options of "extremely well", "very well", "moderately well", "slightly well", or "not well at all"). Mothers were finally presented with a statement representing that some people believe that frequency of NVP predicts the baby will be female. They were asked, "Is this idea familiar to you?", and could respond "Yes, I've heard of it" or "No, I've never heard of it". They were then asked, "Do you believe this idea?", and could respond "Yes, I think it's true" or "No, I don't think it's true".

The first data quality check asked subjects their sex female or male. The second, an implicit test of attention, asked subjects "What color is the sky?", but the instructions below directed subjects to answer the question incorrectly, on purpose, by choosing "yellow" instead of "blue." The third data quality check explicitly asked subjects to indicate how carefully they had completed the survey (with the options of "very carefully", "quite carefully", "moderately carefully", "slightly carefully", and "not at all carefully"), followed by the phrase "Please answer honestly. Your payment does NOT depend on your response to this question." Participants who answered "male", "blue", "green", "red", "moderately carefully", "slightly carefully", or "not at all carefully" were excluded from analysis. See Appendix A in the electronic supplementary materials for the full survey.

Statistics

Variables

Each pregnancy reported in this study was assigned a maternal parity status: if the pregnancy led to the mother's first delivery, it was labeled 'nulliparous'; if the pregnancy led to the mother's second delivery or greater, it

was labeled 'parous'. Geographic cohort was converted to dummy codes, 'India' comparing India to the US, and 'World' comparing World to the US. The previously defined variables of NVP frequency, maternal age, general proneness to nausea, familiarity, and belief in the fold wisdom were also analyzed.

Analyses

A hierarchical multivariate regression was performed to test the predicted effect of fetal gender on NVP and to test the robustness of this effect when other previously identified predictors of NVP (the mother's parity status for that pregnancy, and the mother's age) or potential confounds of this effect (familiarity with the folk wisdom, belief in the folk wisdom, general nausea proneness, and cohort) were included. For these models, β serves as a standardized effect size estimate for individual predictors. For all analyses, a value of $p < 0.05$ (two-tailed) was considered statistically significant. Analyses were performed in SPSS version 25.

Table 1 Participant demographics

Variable	Mean	IQR
Age during pregnancy (years)	26.7	24–29
Births per participant	2	1–3
	Percentage (%)	Ratio
Female babies in cohort	52.2	1326/2543
Male babies in cohort	47.8	1216/2543
Participants in US sub-cohort	50.3	1280/2543
Participants in India sub-cohort	41.7	1061/2543
Participants in World sub-cohort	7.9	202/2543

*Number of male and female babies in cohort does not add up to 2543 because one reported pregnancy did not have a corresponding fetal sex

Results

Participant demographics

3,284 total individuals participated in the study. Participants were excluded from all analyses because: they terminated participation early ($n = 56$), they were male ($n = 245$), they did not pass the implicit attention check ($n = 319$), or they self-reported low attention ($n = 182$), resulting in a total of 741 participants excluded for one or more of these reasons, and yielding data on 4320 pregnancies from 2543 mothers for analysis (see Table 1 for demographic characteristics of the sample). For several of the measurements, participants were able to omit an answer or report they were unsure or did not know the answer; pregnancy reports with these types of missing data were excluded from analyses of those variables. Because, in some cases, these data include multiple pregnancies per mother, analyzing the full sample of pregnancies even after the above exclusions are made violates the assumption of independence made by most types of hypothesis tests. Therefore, we randomly chose a pregnancy from each mother. This set of 2543 independent pregnancies formed our final dataset for analysis.

Does reported frequency of NVP differ by fetal sex?

Yes. At step 1 of our regression analysis, when only fetal sex was entered as a predictor, women were found to have reported higher frequencies of NVP when pregnant with females ($M = 6.35$ on a 1–9 scale) than with males ($M = 6.04$), $\beta = 0.061$, $t(1950) = 2.711$, $p = 0.007$.

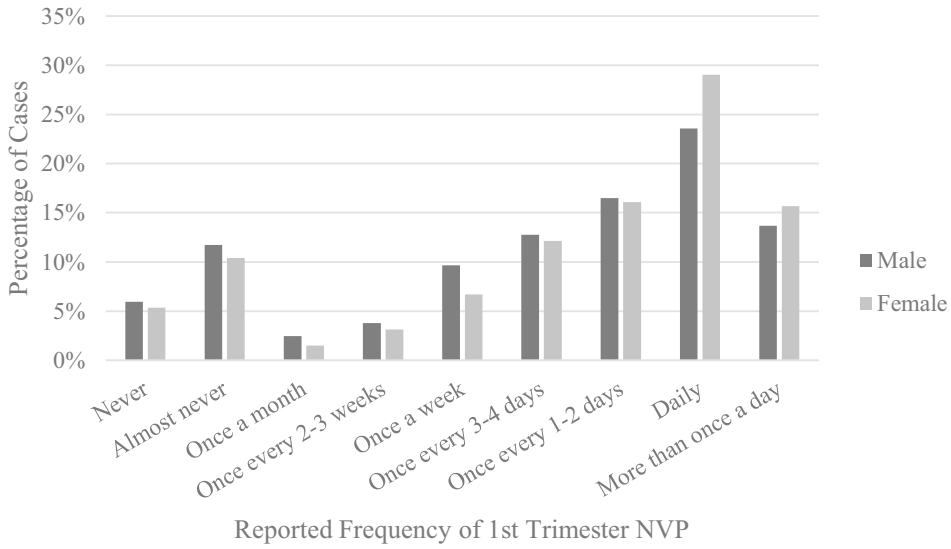

Fig. 1 Recalled frequency of first trimester NVP by fetal sex (male/female)

Inspecting the distribution of reports of NVP frequency separately by sex of fetus (Fig. 1), there appears to be a descriptive difference such that for frequencies of NVP occurring less than daily we see relatively more women gestating sons than daughters, but for frequencies of NVP occurring daily or more than once per day we see relatively more women gestating daughters than sons.

Do other variables present potential confounds for this effect of fetal sex on NVP frequency?

Yes. Consistent with prior literature, a woman's general proneness to nausea, age and parity all predicted NVP frequency (see zero-order correlations in Table 2). Moreover, both familiarity with and belief in the folk wisdom were also related to reported NVP frequency. NVP frequency also differed by cohort, with the highest reports in India, and the lowest reports in the World cohort. Any of these variables singly or in combination could drive a spurious relationship between fetal sex and NVP frequency. This strongly motivated inclusion of these variables in step 2 of the hierarchical regression.

Does the effect of fetal sex on NVP frequency survive controlling for these confounds?

Yes. Fetal sex was found to remain a significant predictor of reported NVP frequency even controlling for all entered variables at step 2 ($\beta = 0.055$, $t(1948) =$, $p = 0.014$); familiarity with the folk wisdom, being in the World cohort, general nausea proneness, maternal age and parity were also significant independent predictors of NVP frequency at step 2; for the full model specification see Table 3.

Discussion

In this study, women who had carried a female fetus reported significantly higher frequencies of NVP during their pregnancies than did women who had carried males. In addition to carrying a female fetus, nulliparity, younger age, and being highly prone to nausea were identified as risk factors for greater frequency of first trimester NVP.

The findings regarding NVP frequency and fetal sex are consistent with current literature on severe NVP that requires hospitalization. Several studies reveal that women presenting with hyperemesis gravidarum have a higher likelihood of

Table 2 Correlation matrix of variables in regression

	Fetal sex	Familiarity	Belief	India	World	General nausea	Maternal age	Parity
NVP frequency	.061**	.066**	.068***	.099***	− .077***	.142***	− .125***	− .115***
Fetal sex		.082***	.077***	− .031	.026	.047*	.002	.002
Familiarity			.337***	− .036***	− .073***	.121***	.017	.077***
Belief				.233***	− .091***	.266***	− .049*	− .026
India					–	.270***	− .028	− .183***
World						− .065**	.010	− .041*
General nausea							− .072***	− .068***
Maternal age								.235***

Statistical significance notated as: $p < .05$*, $p < .01$**, $p < .001$***

Table 3 Regression predicting NVP frequency

Model step	Predictor	b (S.E.)	β	*t*	*p*
1 $R = .061$, $p = .007$	(Constant)	6.157 (0.076)		80.495	< .001
	Fetal sex	0.295 (0.110)	0.061	2.678	.007
2 $R = .229$, $p < .001$	(Constant)	7.818 (0.388)		20.131	< .001
	Fetal sex	0.266 (0.109)	0.055	2.455	.014
	Familiarity	0.273 (0.116)	0.056	2.344	.019
	Belief	− 0.032 (0.154)	− 0.005	0.211	.833
	India (vs. US)	0.206 (0.122)	0.042	1.690	.091
	World (vs. US)	− 0.533 (0.207)	− 0.059	2.576	.010
	General nausea	0.195 (0.043)	0.107	4.509	< .001
	Maternal age	− 0.053 (0.012)	− 0.097	4.256	< .001
	Parity	− 0.820 (0.227)	− 0.084	3.609	< .001

carrying a female fetus than a male fetus [6, 7, 9]; our results suggest that the same trend holds true for pregnant women experiencing less severe but still daily NVP. However, as the frequency of NVP decreases below daily, male fetal sex was more predominant in our cohort. Moreover, our identification of nulliparity, young maternal age, and history of nausea as risk factors for NVP is consistent with previous research [4, 13].

Although the exact pathogenesis of NVP is unknown, several possible factors have been proposed, including various endocrine and metabolic pathways, Helicobacter pylori infection, gastrointestinal dysmotility, and psychosocial factors [4]. One particular endocrine factor that may play a role in NVP and stems from the fetus itself such that it could mediate the effect of fetal sex on NVP is human chorionic gonadotropin (hCG) [14]. hCG production may differ between fetal males and females due to differential placental gene expression. Studies suggest that chromosome-based sex differences in placentas activate the pathways that ultimately lead to emesis [15, 16]. These chromosomal differences result from incomplete X-inactivation and, potentially, epigenetic modifications to the Y chromosome, according to studies of chorionic villi in first trimester placentas [17] and mouse models [18]. Incomplete X-inactivation in the placental gene that regulates hCG production might increase female placental hCG production. Via multiple hormonal mechanisms, this upregulation could ultimately lead to greater incidence of NVP. Incomplete X-inactivation would also explain the spectrum of hCG levels and NVP observed for pregnancies of both fetal sexes, since alterations in epigenetics are not necessarily inherited and may vary from one individual to the next [19]. Nevertheless, the potential for only chromosomal females to have upregulated hCG via incomplete X-inactivation could be the mechanism that results in women pregnant with females experiencing the highest frequency of NVP.

This research adds to the growing body of biomedical literature that utilizes online crowdsourcing as a tool for data collection. Crowdsourcing services have already made a large impact on social science research [20] and have also begun to permeate into biomedical investigation [21]. As a result, several challenges in data quality and external validity have been identified when recruiting participants from online platforms like Amazon's Mechanical Turk [22]. However, online crowdsourcing opens the door to gathering evidence from a large population distributed across the globe. For instance, this study was able to collect data from over 2,500 women living in different parts of the world. Our results add knowledge about a potential risk factor for NVP at a frequency that may not be documented on medical records, and our design illustrates the advantages of online crowdsourcing for collection of data at the intersection of medicine and social science.

Accordingly, this research has several limitations which must be addressed. First and foremost, the electronic survey relied entirely on self-reported accounts of pregnancy experiences, many of which occurred several years in the past. For this reason, the data are subject to memory loss or biased memory recall. Future research could recruit mothers who have given birth more recently, or utilize clinical records of NVP frequency. Second, although the NVP risk factors of maternal age, parity status, and nausea proneness were taken into account, several other potential confounding factors, including BMI, comorbidities, multiple pregnancy, smoking history, and diet (which has been documented to play an especially large role in the incidence of NVP [23–26]) were not examined in this work [4, 13]. Third, our sample was limited to English speaking women with internet access and who participate in online studies, and these may present potential confounding factors that limit the generalizability of our results. Fourth, the survey did not verify whether any participants actually did receive a clinical diagnosis of hyperemesis gravidarum. Solidifying the distinction between daily NVP and hyperemesis gravidarum would add important detail to our findings. Next steps might also assess the relationship between NVP frequency and pregnancy outcomes, taking miscarriage into account.

Conclusion

We present evidence that women gestating a female fetus reported greater frequency of nausea and vomiting during the first trimester of pregnancy than women gestating a male fetus. These findings expand upon the scope of the previously identified association between female fetal sex and hyperemesis gravidarum. Further examination of the cause of this relationship could give insight into its biological origins and clinical implications.

Author contributions NR Young: data analysis, manuscript writing, and manuscript editing. M La Rosa: manuscript editing. SA Mehr: protocol/project development, data collection, and manuscript editing. MM Krasnow: protocol/project development, data collection, data analysis, and manuscript editing.

Funding Not applicable.

Data availability Data are available at: https://osf.io/ecnyx/.

Code availability Syntax for all analyses is available at: https://osf.io/ecnyx/.

Compliance with ethical standards

Conflict of interest Not applicable.

Ethics approval The protocol was approved by the Committee on the Use of Human Subjects in Research at Harvard University (IRB15-2737).

Consent to participate All subjects gave digital informed consent before participating in the study.

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